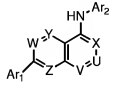
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) A compound of the formula:



or a pharmaceutically acceptable salt ~~or hydrate~~ thereof, wherein:

V, X, W, Y and Z are each independently N or CR_1, with the proviso that at least one of V and X is N;

U is N or CR_2, with the proviso that if V and X are N, then U is CR_2;

R_1 is independently selected at each occurrence from hydrogen, halogen, hydroxy, cyano, amino, -COOH, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxycarbonyl, haloC_1-C_6alkoxy and mono- and di-(C_1-C_6alkyl)amino;

R_2 is:

(i) hydrogen, halogen, cyano or nitro; or

(ii) a group of the formula $–R_c$-M-A-R_y, wherein:

R_c is C_0-C_3alkyl, C_2-C_3alkenyl or C_2-C_3alkynyl, or is joined to R_y or R_z to form a 4- to 10-membered carbocycle or heterocycle that is substituted with from 0 to 2 substituents independently selected from R_b;

M is a bond, O, S, SO, SO_2, C(=O), OC(=O), C(=O)O, O-C(=O)O, C(=O)N(R_z), N(R_z)C(=O), N(R_z)SO_2, SO_2N(R_z), N(R_z), OPO_2(OR_z) or PO_2(OR_z);

A is a bond or C_1-C_8alkyl substituted with from 0 to 3 substituents independently selected from R_b; and

R_y and R_z, if present, are:

(a) independently:

(i) hydrogen or –COOH; or

(ii) C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_3-C_8alkanone, C_2-C_8alkyl ether, a 4- to 10-membered carbocycle or heterocycle, or joined to R_c to form a 4- to 10-membered carbocycle or heterocycle, each of which is substituted with from 0 to 6 substituents independently chosen from R_b; or

(b) joined to form a 4- to 10-membered carbocycle or heterocycle that is substituted with from 0 to 6 substituents independently selected from R_b;

Ar_1 and Ar_2 are independently selected from 5- to 10-membered carbocycles and heterocycles, each of which is substituted with from 0 to 3 substituents independently selected from groups of the formula LR_a;

L is independently selected at each occurrence from a bond, O, $S(O)_m$, C(=O), OC(=O), C(=O)O, O-C(=O)O, $N(R_x)$, C(=O)$N(R_x)$, $N(R_x)$C(=O), $N(R_x)S(O)_m$, $S(O)_mN(R_x)$ and $N[S(O)_mR_x]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C_1-C_8alkyl;

R_a is independently selected at each occurrence from:

(i) hydrogen, halogen, cyano and nitro; and

(ii) C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_2-C_8alkyl ether, mono- and di-(C_1-C_8alkyl)amino and (3- to 10-membered heterocycle)C_0-C_6alkyl, each of which is substituted with from 0 to 6 substituents independently selected from R_b; and

R_b is independently chosen at each occurrence from:

(i) hydroxy, halogen, amino, aminocarbonyl, cyano, nitro, oxo and –COOH; and

(ii) C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkynyl, C_1-C_8alkoxy, C_1-C_8alkanoyl, C_2-C_8alkoxycarbonyl, C_2-C_8alkanoyloxy, C_1-C_8alkylthio, C_2-C_8alkyl ether, phenylC_0-C_8alkyl, phenylC_1-C_8alkoxy, mono- and di-(C_1-C_6alkyl)amino, $(SO_2)C_1$-C_8alkyl, (4- to 7-membered heterocycle)C_0-C_8alkyl, $-PO_3(R_w)_2$ and $-OPO_3(R_w)_2$, wherein each R_w is independently chosen from hydrogen, C_1-C_8alkyl, phenylC_0-C_8alkyl and (5- to 7-membered heterocycle)C_0-C_8alkyl;

wherein each of (ii) is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, aminocarbonyl, cyano, nitro, oxo, -COOH, C_1-C_8alkyl, C_1-C_8alkoxy, C_1-C_8alkoxycarbonyl, C_2-C_8alkanoyloxy, C_1-C_8alkylthio, C_2-C_8alkyl ether, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, phenylC_0-C_8alkyl,

mono- and di-(C_1-C_6alkyl)amino, (SO_2)C_1-C_8alkyl and (5- to 7-membered heterocycle)C_0-C_8alkyl; and

wherein the compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof comprises at least one ~~carboxylic acid,~~ phosphate or phosphonate group.

2. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1, wherein U is C-R_2.

3. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 2, wherein X and V are N.

4. – 7. (Cancelled)

8. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1, wherein W, Y and Z are each CH.

9. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 2, wherein R_2 is a group of the formula –R_c-M-A-R_y, R_c is C_1-C_3alkyl, and R_2 comprises a ~~carboxylic acid,~~ phosphate or phosphonate group.

10. – 12. (Cancelled)

13. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1, wherein Ar_1 and Ar_2 are independently selected from phenyl and 6-membered aromatic heterocycles, each of which is substituted with 0, 1 or 2 substituents independently selected from groups of the formula LR_a.

14. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 13, wherein:

Ar_1 is phenyl or pyridyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, cyano, amino, nitro, mono- and di-(C_1-C_6alkyl)amino, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy and haloC_1-C_6alkoxy; and

Ar_2 is phenyl or pyridyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, cyano, amino, nitro, mono- and di-(C_1-C_6alkyl)amino, C_1-C_6alkyl, haloC_1-C_6alkyl, cyanoC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkyl ether, C_1-C_6alkanoyl, $-(SO_2)R_d$, $-N(R_x)S(O)_mR_d$, and $-N[S(O_m)R_x]S(O)_mR_d$; wherein m is 1 or 2, R_x is hydrogen or C_1-C_6alkyl, and R_d is C_1-C_6alkyl, haloC_1-C_6alkyl, amino, mono- or di-(C_1-C_6alkyl)amino or a 5- to 10-membered, N-linked heterocyclic group, each of which R_d is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, mono- and di-(C_1-C_6alkyl)amino, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy and haloC_1-C_4alkoxy.

15. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 13, wherein:

Ar_1 is pyridyl, unsubstituted or substituted with halogen, cyano, C_1-C_4alkyl or haloC_1-C_4alkyl; and

Ar_2 is phenyl or pyridyl, substituted with from 0 to 2 substituents independently chosen from halogen, C_1-C_4alkyl, cyanoC_1-C_4alkyl, haloC_1-C_4alkyl, C_2-C_6alkyl ether and groups of the formula $-(SO_2)R_d$, wherein R_d is C_1-C_4alkyl or haloC_1-C_4alkyl.

16. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 13, wherein:

Ar_1 is phenyl, unsubstituted or substituted with halogen, cyano, C_1-C_4alkyl or haloC_1-C_4alkyl; and

Ar_2 is phenyl or pyridyl, substituted with from 0 to 2 substituents independently chosen from halogen, C_1-C_4alkyl, cyanoC_1-C_4alkyl, haloC_1-C_4alkyl, C_2-C_6alkyl ether and groups of the formula $-(SO_2)R_d$, wherein R_d is C_1-C_4alkyl or haloC_1-C_4alkyl.

17. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 13, wherein:

Ar_1 is pyridin-2-yl, 3-methyl-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl or 3-halo-pyridin-2-yl; and

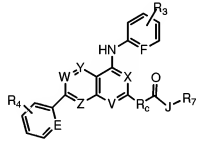
Ar_2 is phenyl, pyridin-2-yl or pyridin-3-yl, each of which is substituted at the *para*-position with halogen, cyano, methyl, ethyl, propyl, isopropyl, *t*-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1-methyl-ethyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, propane-2-sulfonyl, trifluoromethanesulfonyl or 2,2,2-trifluoroethanesulfonyl.

18. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 13, wherein:

Ar_1 is phenyl, 2-methyl-phenyl, 2-trifluoromethyl-phenyl or 2-halo-phenyl; and

Ar_2 is phenyl, pyridin-2-yl or pyridin-3-yl, each of which is substituted at the *para*-position with halogen, cyano, methyl, ethyl, propyl, isopropyl, *t*-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1-methyl-ethyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, propane-2-sulfonyl, trifluoromethanesulfonyl or 2,2,2-trifluoroethanesulfonyl.

19. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 2, wherein the compound has the formula:



wherein:

R_c is C_0-C_2alkyl;

J is O or $N(R_z)$;

R_z is:

(a) hydrogen;

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6alkanone, C_2-C_6alkyl ether, or a 4- to 10-membered carbocycle or heterocycle, each of which is substituted with from 0 to 6 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, -COOH, aminocarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-

C_8alkoxycarbonyl, C_2-C_8alkanoyloxy, C_1-C_8alkylthio, C_2-C_8alkyl ether, and mono- and di-(C_1-C_6alkyl)amino; or

(c) joined to R_7 to form a 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 6 substituents independently selected from halogen, hydroxy, cyano, amino, nitro, -COOH, aminocarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_8alkoxycarbonyl, C_2-C_8alkanoyloxy, C_1-C_8alkylthio, C_2-C_8alkyl ether, and mono- and di-(C_1-C_6alkyl)amino;

E and F are independently CH or N;

R_3 represents from 0 to 2 substituents independently chosen from halogen, cyano, -COOH, C_1-C_6alkyl, haloC_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_2-C_6alkyl ether, C_1-C_6alkanoyl, aminosulfonyl, mono- and di-(C_1-C_8alkyl)aminosulfonyl, (C_1-C_8alkyl)sulfonyl, amino, and mono- and di-(C_1-C_6alkyl)amino;

R_4 represents from 0 to 2 substituents independently chosen from halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, mono- and di-(C_1-C_6alkyl)amino, aminosulfonyl, and mono- and di-(C_1-C_8alkyl)aminosulfonyl; and

R_7 is:

(i) hydrogen;

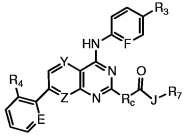
(ii) C_1-C_6alkyl, phenyl or 5- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, -COOH, aminocarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_8alkoxycarbonyl, C_2-C_8alkanoyloxy, C_1-C_8alkylthio, C_2-C_8alkyl ether, mono- and di-(C_1-C_6alkyl)amino; or

(iii) joined to R_z to form an optionally substituted 5- to 7-membered heterocycle; and

wherein the group designated:

comprises at least one carboxylic acid group.

20. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 19, wherein the compound has the formula:



wherein:

Y and Z are independently CH or N;

R_3 is halogen, cyano, -COOH, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, or mono- or di-(C_1-C_6alkyl)amino;

R_4 is halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, or mono- or di-(C_1-C_6alkyl)amino; and

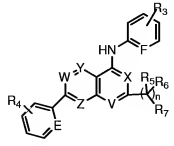
R_7 is (i) hydrogen; (ii) C_1-C_6alkyl substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, -COOH, C_1-C_6alkoxy, and mono- and di-(C_1-C_6alkyl)amino; or (iii) joined to R_z to form an optionally substituted 5- to 7-membered heterocycle.

21. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 20, wherein J is O.

22. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 21, wherein R_7 is hydrogen.

23. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 20, wherein J is NH.

24. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 2, wherein the compound has the formula:



wherein:

E and F are independently CH or N;

R_3 represents from 0 to 2 substituents independently chosen from halogen, cyano, -COOH, C_1-C_6alkyl, haloC_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_2-C_6alkyl ether, C_1-C_6alkanoyl, aminosulfonyl, mono- and di-(C_1-C_8alkyl)aminosulfonyl, (C_1-C_8alkyl)sulfonyl, amino, and mono- and di-(C_1-C_6alkyl)amino;

R_4 represents from 0 to 2 substituents independently chosen from halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, mono- and di-(C_1-C_6alkyl)amino, aminosulfonyl, and mono- and di-(C_1-C_8alkyl)aminosulfonyl;

each R_5 and R_6 is independently selected from hydrogen, hydroxy and C_1-C_8alkyl substituted with from 0 to 2 substituents independently selected from R_d;

R_7 is:

(i) –COOH; or

(ii) C_2-C_8alkoxycarbonyl, C_2-C_8alkanoyloxy, C_1-C_8alkoxy, mono- or di-(C_1-C_8alkyl)amino, or a 5- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from R_d; or

(iii) $-PO_3(R_w)_2$ or $–OPO_3(R_w)_2$, wherein each R_w is independently chosen from:

(a) hydrogen; and

(b) C_1-C_8alkyl, phenylC_0-C_8alkyl and (5- to 7-membered heterocycle)C_0-C_8alkyl each of which is substituted with from 0 to 3 substituents independently chosen from R_d;

n is 0, 1, 2 or 3; and

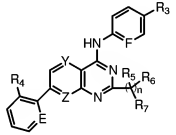
each R_d is independently chosen from:

(i) halogen, hydroxy, cyano, amino, nitro, -COOH; and

(ii) C_1-C_4alkyl, C_2-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4alkanoyl, C_2-C_4alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_4alkylthio, C_2-C_4alkyl ether, and mono- and di-(C_1-C_4alkyl)amino, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino and –COOH; and

wherein R_7 is a ~~carboxylic acid,~~ phosphate or phosphonate group or at least one of R_5, R_6 or R_7 comprises at least one substituent selected from a ~~carboxylic acid,~~ phosphate or phosphonate group.

25. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 24, wherein the compound has the formula:



wherein:

Y and Z are independently CH or N;

R_3 is halogen, cyano, -COOH, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, or mono- or di-(C_1-C_6alkyl)amino;

R_4 is halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, or mono- or di-(C_1-C_6alkyl)amino;

each R_5 and R_6 is independently hydrogen or methyl; and

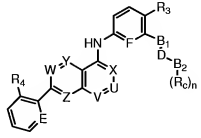
R_7 is:

~~(i) –COOH;~~

~~(ii) C_1-C_8alkoxy, C_1-C_8alkoxycarbonyl, pyrrolidine, piperidine, piperazine or morpholine, each of which is substituted with from 1 to 3 substituents independently chosen from R_d, wherein at least one occurrence of R_d is a carboxylic acid group; or~~

~~(iii)~~ $-PO_3(R_w)_2$ or $–OPO_3(R_w)_2$.

26. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 2, wherein the compound has the formula:



wherein:

E and F are independently CH or N;

R_3 represents from 0 to 2 substituents independently chosen from halogen, cyano, -COOH, C_1-C_6alkyl, haloC_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_2-C_6alkyl ether, C_1-C_6alkanoyl, aminosulfonyl, mono- and di-(C_1-C_8alkyl)aminosulfonyl, (C_1-C_8alkyl)sulfonyl, amino, and mono- and di-(C_1-C_6alkyl)amino;

R_4 represents from 0 to 2 substituents independently chosen from halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, amino, mono- and di-(C_1-C_6alkyl)amino, aminosulfonyl, and mono- and di-(C_1-C_8alkyl)aminosulfonyl;

B_1 is O, NH or S;

D is –C(=O)- or C_2-C_3alkyl, unsubstituted or substituted with a keto group;

and

B_2 is:

(a) O or S; in which case n is 1, and R_c is hydrogen, PO_3H_2, PO_3H(alkyl), PO_3(alkyl)$_2$, C_1-C_6alkyl, or C_2-C_6alkyl ether, each of which alkyl moiety is substituted with from 0 to 3 substituents independently selected from R_d; or

(b) N, in which case n is 2, and

(i) R_c is independently chosen at each occurrence from hydrogen and C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, each of which is substituted with from 0 to 3 substituents selected from R_d; or

(ii) both R_c moieties are joined to form, with B_2, a 5- to 8-membered heterocycloalkyl that is substituted with from 0 to 3 substituents selected from R_d; and

each R_d is independently:

(i) halogen, hydroxy, cyano, amino, nitro, -COOH; and

(ii) C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4alkanoyl, C_2-C_4alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_4alkylthio, C_2-C_4alkyl ether, or mono- or di-(C_1-C_4alkyl)amino, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino and –COOH; and

wherein the group designated:

$$-B_1-D-B_2-(R_c)_n$$

comprises at least one carboxylic acid, phosphate or phosphonate group.

27. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ according to claim 26, wherein;

B_1 is O; and

either:

(i) D is $–CH_2-CH_2-$ and $-B_2-(R_c)_n$ is:

(a) -COOH, $-O-PO_3H_2$, or $-PO_3H_2$; or

(b) pyrrolidine, piperidine, piperazine or morpholine, each of which is substituted with –COOH; or

(ii) D is $–CH_2-C(=O)-$ and $-B_2-(R_c)_n$ is:

(a) –OH; or

(b) pyrrolidine, piperidine, piperazine or morpholine, each of which is substituted with –COOH.

28. - 29. (Cancelled)

30. (Currently amended) A compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1 wherein the compound has an IC_{50} value of 10 nanomolar or less in a capsaicin receptor calcium mobilization assay.

31. (Currently amended) A pharmaceutical composition, comprising a therapeutically effective amount of at least one compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1 in combination with a physiologically acceptable carrier or excipient.

32. (Cancelled)

33. (Currently amended) A method for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell expressing a capsaicin receptor with at least one compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1, and thereby reducing calcium conductance of the capsaicin receptor.

34. - 40. (Cancelled)

41. (Currently amended) A method for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro*, the method comprising contacting capsaicin receptor with at least one compound or pharmaceutically acceptable salt ~~or hydrate~~ thereof according to claim 1, under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to capsaicin receptor.

42. - 73. (Cancelled)